Bronchoprovocation / Methacholine Challenge Testing

Getting with the 2017 Task Force Report
ERS Technical Standard

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Pulmonary Diagnostic Labs

September 2019 - Focus Conference
Conflicts of Interest

• Faculty for MGC Diagnostics Cardiopulmonary seminar.
• Education consultant for ERT.

• The University of Wisconsin Pulmonary Lab uses a mix of PFT systems and devices including: MGC Diagnostics, Jaeger, Vyaire, Sensor Medics, ndd, nSpire, Ecomedics, Ganzorn, Hans Rudolph, Circassia....
1. Review major recommendations from the new ERS technical standard.
2. Review the primary reason for performing a methacholine challenge test.
3. Understand the indications and contraindications.
4. Learn how to integrate “characterized” nebulizers or dosimeters, using tidal breathing methods and output the PD20.
References


• Characterizing Nebulizer Performance for Methacholine Challenge Testing. AJRCCM Articles in Press. Published 30 Aug 2018 as 10.1164/rccm.201805-0942ED

• 2016 ATS Pulmonary Function Laboratory Management and Procedure Manual

ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests

Allan L. Coates¹, Jack Wanger², Donald W. Cockcroft³, Bruce H. Culver⁴ and the Bronchoprovocation Testing Task Force: Kai-Håkon Carlsen⁵, Zuzana Diamant⁶,⁷, Gail Gauvreau⁸, Graham L. Hall⁹, Teal S. Hallstrand⁹, Ildiko Horvath¹⁰, Frans H.C. de Jongh¹¹, Guy Joos¹², David A. Kaminsky¹³, Beth L. Laube¹⁴, Joerg D. Leuppi¹⁵ and Peter J. Sterk¹⁶

Major Recommendations

• Use **provocative dose** (PD20): allows comparable results

• **Delivery devices**: nebulizer or dosimeter should be well characterized for dose-output steps.

• **Inhalation protocol**: Tidal breathing, one min or more if using a breath activated neb or dosimeter with a breath count; no deep breathing.

• **Dose steps**: Starting dose 1-3 ug with doubling or quadrupling steps…starting dose depends on efficiency of the delivery device
Principle / goal of methacholine challenge testing

- Assess **airway responsiveness**—pulmonary function
  - During exposure to increasing dose or concentration of methacholine chloride, what changes are seen in airway function?
  - Provocative dose that results in a 20% fall in FEV1 (PD20)

- Options
  - Airway resistance (Decrease in sGaw: PD40)
  - Oscillometry (Increase in R5 or resonant freq)
What is Airway Hyper Responsiveness?

- An increased sensitivity and exaggerated response to non-allergic stimuli.
- AHR is associated with asthma.
- AHR is also seen in other diseases associated with airway inflammation and obstruction.
• AHR is common in athletes (cold related sports)
• AHR may increase during exacerbations
• AHR may decrease during Rx with antiinflammatory medications.
• AHR may be absent during asymptomatic periods.
Value of Methacholine Test

- “Methacholine challenge testing is more useful in excluding the diagnosis of asthma than in establishing one because its negative predictive power is greater than its positive predictive power.”

- Pretest probability: wheezing, dyspnea, chest tightness, cough…
  - With exposure to cold
  - After exercise
  - During respiratory infections
  - Following inhalant exposures in workplace
Clinical Indications

- **Assess airway responsiveness**
- Spirometry before and after bronchodilators has not helped establish a diagnosis.
- **Contribute** to a dx of asthma
- Evaluation of occupational asthma
- Evaluate risk of developing asthma
- Assess severity of asthma
- Assess response to therapy
Contraindications

*Things that may alter the quality of the test or may put the patient at greater risk / discomfort.

### TABLE 1 Contraindications for bronchial challenge testing

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Airflow limitation</strong></td>
<td>FEV₁ &lt; 60% predicted (adults or children) or 1.5 L (adults)</td>
</tr>
<tr>
<td></td>
<td>FEV₁ &lt; 75% predicted (adults or children) for exercise or eucapnic voluntary hyperpnoea challenge</td>
</tr>
<tr>
<td><strong>Spirometry quality</strong></td>
<td>Inability to perform acceptable and repeatable spirometry manoeuvres throughout the test procedure</td>
</tr>
<tr>
<td><strong>Cardiovascular problems</strong></td>
<td>Myocardial infarction or stroke in last 3 months</td>
</tr>
<tr>
<td></td>
<td>Uncontrolled hypertension</td>
</tr>
<tr>
<td></td>
<td>Known aortic aneurysm</td>
</tr>
<tr>
<td></td>
<td>Recent eye surgery or intracranial pressure elevation risk</td>
</tr>
<tr>
<td><strong>General</strong></td>
<td>Inability to perform any of the testing manoeuvres, such as inhaling the challenge agent consistently or difficulty with exercise on treadmill or bike; most commonly in young children or elderly patients</td>
</tr>
</tbody>
</table>
Contraindications* ERS Technical Standard

• **Low FEV1** (relative contraindication, children and adults)
  – FEV1 < 1.5 L (adults)
  – FEV1 < 60% of predicted (adults or children)
  – FEV1 < 75% of pred (adults or children) exercise or EVH.

• Obstructive defect at baseline testing
  – Low FEV1 and FEV1/FVC ratio
  – Already documented response to BDs (12% and 200 mL)

• **Poor quality spirometry**
  – A quality BCT relies on acceptable spirometry. *Unreliable baseline values or poor effort…reschedule/eval alternative endpoint.*
Contraindications*

- Cardiovascular problems:
  - Uncontrolled hypertension (>200 systolic / >100 mmHg diastolic)
  - Recent MI, stroke, arterial hypoxemia, known aortic aneurysm
- Recent eye surgery or any condition where increased intracranial pressure would be harmful is a contraindication. (absolute)
  - *Lasix surg, detached retina, cerebral aneurysm*
- Relative contraindications: Pregnancy and cholinesterase inhibitor meds for myasthenia gravis
- Severe airflow limitation (FEV1< 50% pred or <1.0 L)
Staff and Patient Safety

- Minimize staff exposure to methacholine aerosol (distance, mask)
- Consider using a breath-actuated neb or dosimeter
  - Expiratory filters are available for BAN and APS devices.
- Use a mouthpiece not facemask to deliver methacholine.
- Test in a room with at least 2 complete air exchanges, exhaust ventilation or HEPA filtration.
- Consider excluding staff with AHR

- Staff should be **well trained**
  - Up to date competencies
  - Senior staff or MD available
  - Minimize interruptions
- Stay with patient during entire test
- Post test FEV1 within **10% of baseline**
- Rescue medications must be in testing room (Albuterol, epinephrine)
- Stethoscope, pulse oximeter, oxygen.
Staff Qualifications (minimum)*

<table>
<thead>
<tr>
<th>TABLE 2 Qualifications to perform bronchial challenge tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>The technician/respiratory scientist should:</td>
</tr>
<tr>
<td>1) Have background knowledge of respiratory diseases, be familiar with this guideline and knowledgeable about specific test procedures</td>
</tr>
<tr>
<td>2) Be capable of managing the equipment including set-up, calibration checks, verification of proper function, maintenance, hygiene and cleaning</td>
</tr>
<tr>
<td>3) Be proficient at spirometry</td>
</tr>
<tr>
<td>4) Know the contraindications to bronchial challenge testing</td>
</tr>
<tr>
<td>5) Be familiar with safety and emergency procedures</td>
</tr>
<tr>
<td>6) Know when to stop further testing</td>
</tr>
<tr>
<td>7) Be proficient with the administration of inhaled bronchodilators and evaluation of the response to them</td>
</tr>
</tbody>
</table>

- 4 days of hands on training*
- 20 supervised tests for new technician/ respiratory scientist*
Recommendations for withholding medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Minimum time interval from last dose to MCT h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting β-agonists in conventional inhaled doses (e.g. albuterol 200 µg)</td>
<td>6</td>
</tr>
<tr>
<td>Long-acting β-agonists (e.g. salmeterol)</td>
<td>36</td>
</tr>
<tr>
<td>Ultra-long-acting β-agonists (e.g. indacaterol, vilanterol, olodaterol)</td>
<td>48</td>
</tr>
<tr>
<td>Ipratropium (Atrovent 40 µg)</td>
<td>12</td>
</tr>
<tr>
<td>Long-acting anti-muscarinic agents</td>
<td>≥168</td>
</tr>
<tr>
<td>Oral theophylline</td>
<td>12–24</td>
</tr>
</tbody>
</table>
Don’t worry about…

• Flu shots
• Menstrual cycle or contraceptives
• Normal dietary intake of caffeinated products
• Antihistamines
Patient preparation…scheduling*

- List of meds to avoid.
- Withhold: Alcohol 4 hrs, smoking 1 hr.

- Asthma meds (except bronchodilators) may be continued if the intent is to monitor the response to therapy.

- Single dose (cromones, inhaled corticosteroids, leukotriene modifiers) have minimal effect….if goal is to be free of antiinflammatory effect…4-8 weeks
## Medication withholding-bronchoprovocation

<table>
<thead>
<tr>
<th>6 hours</th>
<th>12 hours</th>
<th>24 hours</th>
<th>36 hours</th>
<th>48 hours</th>
<th>1 week</th>
<th>4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short acting bronchodilator</td>
<td>Short acting anticholinergics</td>
<td>Oral</td>
<td>Long acting bronchodilators</td>
<td>Ultra long acting Bronchodilators</td>
<td>Long acting anti-muscarinic agents</td>
<td>Cromones</td>
</tr>
<tr>
<td>Albuterol</td>
<td>Ipratropium</td>
<td>Theophylline</td>
<td>Salmeterol</td>
<td>Fluticasone/Vilanterol</td>
<td>Breo Ellipta®</td>
<td>Anti-cholinergics</td>
</tr>
<tr>
<td>Proair®</td>
<td>Atrovent®</td>
<td></td>
<td>Serevent Diske</td>
<td>Indacaterol</td>
<td>Arcapta健</td>
<td>Umeclidinium/</td>
</tr>
<tr>
<td>Proventil®</td>
<td>Combivent®</td>
<td></td>
<td>Diskus™</td>
<td>Neohaler®</td>
<td>Neohaler®</td>
<td>Vilanterol</td>
</tr>
<tr>
<td>Ventolin®</td>
<td>Respimat®</td>
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<td>Formoterol™</td>
<td>Olodaterol</td>
<td>Striverdi健</td>
<td>Breve Ellipta®</td>
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<td>Xopenex®</td>
<td>DuoNeb®</td>
<td></td>
<td>Perforomist®</td>
<td>Respimat®</td>
<td>Respimat®</td>
<td>Glycopyrrolate/</td>
</tr>
<tr>
<td><strong>Pirbuterol</strong></td>
<td><strong>Ipratropium</strong></td>
<td></td>
<td><strong>Salmeterol</strong></td>
<td><strong>Fluticasone</strong></td>
<td><strong>Breo Ellipta®</strong></td>
<td><strong>formoterol</strong></td>
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<tr>
<td><strong>Maxair®</strong></td>
<td><strong>Atrovent®</strong></td>
<td></td>
<td><strong>Serevent</strong></td>
<td><strong>Indacaterol</strong></td>
<td><strong>Arcapta健</strong></td>
<td>**Umeclidinium/</td>
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<td><strong>Diskus™</strong></td>
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<td><strong>Olodaterol</strong></td>
<td><strong>Striverdi健</strong></td>
<td><strong>Breve Ellipta®</strong></td>
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<td><strong>Respimat®</strong></td>
<td><strong>Respimat®</strong></td>
<td>**Glycopyrrolate/</td>
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<td><strong>indacaterol</strong></td>
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<td><strong>Umeclidinium</strong></td>
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<td><strong>Glycopyrrolate</strong></td>
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<td><strong>Seebri Neohaler®</strong></td>
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<td></td>
<td><strong>Umeclidinium</strong></td>
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<td><strong>Incruise Ellipta®</strong></td>
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<td></td>
<td></td>
<td><strong>Acilinium bromide</strong></td>
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<td></td>
<td><strong>Tudorza Pressair®</strong></td>
</tr>
</tbody>
</table>

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**Anticholinergics**
- Ipratropium
- Atrovent®
- Combivent®
- Respimat®
- DuoNeb®

**Bronchodilators**
- Albuterol
- Proair®
- Proventil®
- Ventolin®
- Xopenex®
- Pirbuterol
- Maxair®

**Cromones**
- Ipratropium
- Atrovent®
- Combivent®
- Respimat®
- DuoNeb®

**Antiepileptics**
- Theophylline

**Inhaled Corticosteroids**
- Flunisolide
- Aerospan®
- Ciclesonide
- Alveso HFA®
- Fluticasone furoate
- Arnuity Ellipta®
- Mometasone furoate
- Asmanex® HFA®
- Asmanex® Twisthaler
- Fluticasone propionate
- Flovent Diske® / HFA
- Budesonide
- Pulmicort Flexhaler®
- Beclamethasone
- QVAR HFA®
- Fluticasone/salmeterol
- Advair Diske® / HFA
- Mometasone/formoterol
- Dulera HFA®
- Budesonide/formoterol
- Symbicort HFA®
Methacholine Chloride

- Established compound used to assess airway hyperresponsiveness.

- Made in Canada by Methapharm
  - FDA approved

- White, water soluble powder, hygroscopic

- 20 mL vial contains 100 mg dry powder of Methacholine chloride USP

- Parasympathomimetic (cholinergic) bronchoconstrictive agent, inhalation only, for diagnostic purposes.

https://provocholine.com  Methapharm.com
Solution preparation*

• Reconstitution should be by pharmacist or other well trained person using sterile technique.

• Precise mixing is critical for accurate results and patient safety.
  • Diluent can be sterile normal saline with or without phenol.

• Solutions should be warmed to room temperature before use.
Solution preparation

- Powder form: storage at room temp up to 3 years 59-86 F (15-30 C)
- Refrigerate reconstituted solutions at 36 -46° F (2- 8 C) for no more than 2 weeks
- Lowest concentrations are generally prepared the day of the challenge.
# Dilution Schedules

## Quadrupling and Doubling

<table>
<thead>
<tr>
<th>Label strength</th>
<th>Take</th>
<th>Add NaCl (0.9%)</th>
<th>Obtain dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example of a dilution schedule for quadrupling concentrations</td>
<td>100 mg</td>
<td>6.25 mL</td>
<td>A: 16 mg·mL⁻¹</td>
</tr>
<tr>
<td>100 mg</td>
<td>3 mL of dilution A</td>
<td>9 mL</td>
<td>B: 4 mg·mL⁻¹</td>
</tr>
<tr>
<td>3 mL of dilution B</td>
<td>9 mL</td>
<td>C: 1 mg·mL⁻¹</td>
<td></td>
</tr>
<tr>
<td>3 mL of dilution C</td>
<td>9 mL</td>
<td>D: 0.25 mg·mL⁻¹</td>
<td></td>
</tr>
<tr>
<td>3 mL of dilution D</td>
<td>9 mL</td>
<td>E: 0.0625 mg·mL⁻¹</td>
<td></td>
</tr>
<tr>
<td>3 mL of dilution E</td>
<td>9 mL</td>
<td>F: 0.015625 mg·mL⁻¹</td>
<td></td>
</tr>
<tr>
<td>Example of a dilution schedule for doubling doses</td>
<td>100 mg</td>
<td>6.25 mL</td>
<td>A: 16 mg·mL⁻¹</td>
</tr>
<tr>
<td>100 mg</td>
<td>3 mL of dilution A</td>
<td>3 mL</td>
<td>B: 8 mg·mL⁻¹</td>
</tr>
<tr>
<td>3 mL of dilution B</td>
<td>3 mL</td>
<td>C: 4 mg·mL⁻¹</td>
<td></td>
</tr>
<tr>
<td>3 mL of dilution C</td>
<td>3 mL</td>
<td>D: 2 mg·mL⁻¹</td>
<td></td>
</tr>
<tr>
<td>3 mL of dilution D</td>
<td>3 mL</td>
<td>E: 1 mg·mL⁻¹</td>
<td></td>
</tr>
<tr>
<td>3 mL of dilution E</td>
<td>3 mL</td>
<td>F: 0.5 mg·mL⁻¹</td>
<td></td>
</tr>
<tr>
<td>3 mL of dilution F</td>
<td>3 mL</td>
<td>G: 0.25 mg·mL⁻¹</td>
<td></td>
</tr>
<tr>
<td>3 mL of dilution G</td>
<td>3 mL</td>
<td>H: 0.125 mg·mL⁻¹</td>
<td></td>
</tr>
<tr>
<td>3 mL of dilution H</td>
<td>3 mL</td>
<td>I: 0.0625 mg·mL⁻¹</td>
<td></td>
</tr>
<tr>
<td>3 mL of dilution I</td>
<td>3 mL</td>
<td>J: 0.03125 mg·mL⁻¹</td>
<td></td>
</tr>
</tbody>
</table>

Using a 100-mg vial of methacholine and NaCl (0.9%) for diluent, the table shows the range of concentrations available to produce appropriate dose steps using examples of dilutions with quadrupling and doubling increases. If necessary, alternative concentrations can be produced from a different initial dilution step. For example, adding 5 mL of diluent to 100 mg methacholine would produce dilution A of 20 mg·mL⁻¹ and adding 8.3 mL of diluent to 100 mg methacholine would produce dilution A of 12 mg·mL⁻¹.
Delivery devices*

• “Any suitable nebulizer or dosimeter may be used”
• Vendor must provide characterization of nebulizer output, and particle size.
• Vendor info will allow table of concentration-dose steps for inhalation protocol.
Stand alone Dosimeters

Salter Dosimeter
Aerosol Generating Device
for precise administration of broncho-provocation agents

Precise Control of Nebulizer “on” time

A simple explanation to calculate dose delivered:
Example: assuming the output of a nebulizer is 45 ml/min when driven by a compressed gas source at 50 psi 7 LPM. For a given medication concentration refer to the desired dose of Broncho-provocation agent.

The dose output may then be calculated as follows:
Dose Output= (concentration of medication) x (nebulizer output) x (nebulization duration)
Dose Output= mg/ml x ml/min x min
Dosing: *protocols/methods/devices*

- Two minute tidal breathing
- Multi-breath dosimeter
- Tidal breathing
- BAN (minute or breaths)

**Abstract:** Developing Alternative Delivery System for Methacholine Challenge Tests, Allan L Coates, Kitty Leung, Sharon Dell, Bruce Culver

- El-Gammal, Killian, Scime, et al.; Relationship between Wright and AeroElipse Nebulizers 2015

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**Images:** ATS Guidelines for Methacholine and Exercise Challenge Testing 1999, AE BAN Monaghan Medical Corp

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**Figure 1:** Schematic diagram illustrating typical nebulizer configurations for both the 2-min tidal breathing protocol (A, an English Wright nebulizer) and the five-breath dosimeter protocol (B, a DeVilbiss model 646 nebulizer). Both include an exhalation filter. Other models of nebulizers may be substituted (see Section II, H).
Dose steps*

• Dose one: 1-3 µg
  – “with subsequent doubling or quadrupling steps”
• Dose two: ___µg
• Dose three: ___ µg
• Dose four: ___µg

• No dose should >800 µg
• No need to mirror Wright neb dosing but it can be used as a reference.
NOTE: This editorial is not a component of the ERS technical standard on bronchial challenge testing that was endorsed by the American Thoracic Society in March 2017. Therefore, while the information contained within is consistent with the ERS technical statement, the editorial should not be considered an official position of either the ERS or ATS.
Benefits of this publication...

- Clarifies / reduces uncertainty on how to perform testing
- Emphasizes / explains why “dose not concentration”… depending on the neb used.
- Helps/signals manufactures to characterize nebulizers for use for methacholine testing.
- Details how using a mechanical simulator, albuterol and UV spectrophotometry can be used to determine neb output.
- Stresses using change in neb weight to calculate output is not acceptable.
- Supports use of single use nebulizers for challenge testing.
- Provides a protocol example
# Table – One Example of a Methacholine Challenge Protocol Using an AeroEclipse™ BAN II

<table>
<thead>
<tr>
<th>Methacholine Concentration (mg/ml)</th>
<th>Methacholine Dose (ug)</th>
<th>Inhalation Time</th>
<th>Spirometry Testing Time After Inhalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diluent</td>
<td>0.0</td>
<td>1 minute</td>
<td>30 sec, 90 sec</td>
</tr>
<tr>
<td>*0.0156</td>
<td>2.0</td>
<td>1 minute</td>
<td>30 sec, 90 sec</td>
</tr>
<tr>
<td>0.0313</td>
<td>4.0</td>
<td>1 minute</td>
<td>30 sec, 90 sec</td>
</tr>
<tr>
<td>0.0625</td>
<td>8.0</td>
<td>1 minute</td>
<td>30 sec, 90 sec</td>
</tr>
<tr>
<td>0.1250</td>
<td>16.0</td>
<td>1 minute</td>
<td>30 sec, 90 sec</td>
</tr>
<tr>
<td>0.2500</td>
<td>32.1</td>
<td>1 minute</td>
<td>30 sec, 90 sec</td>
</tr>
<tr>
<td>0.5000</td>
<td>64.1</td>
<td>1 minute</td>
<td>30 sec, 90 sec</td>
</tr>
<tr>
<td>1.0000</td>
<td>128.3</td>
<td>1 minute</td>
<td>30 sec, 90 sec</td>
</tr>
<tr>
<td>2.0000</td>
<td>256.5</td>
<td>1 minute</td>
<td>30 sec, 90 sec</td>
</tr>
<tr>
<td>4.0000</td>
<td>513.0</td>
<td>1 minute</td>
<td>30 sec, 90 sec</td>
</tr>
</tbody>
</table>

*Note that Methapharm, Inc. is still in the process of validating measurement of this concentration.*
### Example: BAN Neb dosing – 1 Min Tidal

<table>
<thead>
<tr>
<th>Methacholine Concentration (mg/mL)</th>
<th>Methacholine Dose (ug)</th>
<th>Inhalation Time</th>
<th>Spirometry Time After Inhalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diluent</td>
<td>0</td>
<td>1 minute</td>
<td>30 sec, 90 sec</td>
</tr>
<tr>
<td>0.0156 mg/mL</td>
<td>2.0</td>
<td>1 minute</td>
<td>30 sec, 90 sec</td>
</tr>
<tr>
<td>0.0625 mg/mL</td>
<td>8</td>
<td>1 minute</td>
<td>30 sec, 90 sec</td>
</tr>
<tr>
<td>0.250 mg/mL</td>
<td>32.1</td>
<td>1 minute</td>
<td>30 sec, 90 sec</td>
</tr>
<tr>
<td>1.0 mg/mL</td>
<td>128.3</td>
<td>1 minute</td>
<td>30 sec, 90 sec</td>
</tr>
<tr>
<td>4.0 mg/mL</td>
<td>513</td>
<td>1 minute</td>
<td>30 sec, 90 sec</td>
</tr>
</tbody>
</table>
AeroEclipse II BAN Option

- Output is robust
- Nebulization can be set to breath actuated or continuous.
- Flow rate 7 L/s yields 0.39 mL/min
- Output as long as inspiratory flow is >13 L/min
- Might have limitations if used with very small children because of flow req.

- Methods?
  - 1 minute with 4 mg/mL max concentration
  - 6 breath /actuated mode option using up to 16mg/mL concentration
BAN tips

- Recommended flow rate of 7-8 Lpm
- 50 psi gas source?
- Set to breath actuated mode
- Use time or limit number of breaths
- Compressor:
  - Precision Med #PM15P
  - Click flow meter #7MFA1002
Example: Vmax BAN 6 Breath Tidal

- **Test Level**: Pre, Baseline, Post
- **Test Protocol**: PC20 Methacholine, PC20 Antigen (ATS), BAN 6 Breath Tidal
- **Protocol Name**: BAN 6 Breath Tidal
- **Provocation Agent**: Methacholine

### Level and Concentration/Dose Table

<table>
<thead>
<tr>
<th>Level</th>
<th>Concentration / Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.6</td>
</tr>
<tr>
<td>2</td>
<td>10.6</td>
</tr>
<tr>
<td>3</td>
<td>42.2</td>
</tr>
<tr>
<td>4</td>
<td>178</td>
</tr>
<tr>
<td>5</td>
<td>660</td>
</tr>
</tbody>
</table>

*Warning the user when a change to the protocol level changes the nebulizer concentration.*
Bronchoprovocation Report

Protocol: BAN 6 Breath Tidal

<table>
<thead>
<tr>
<th>Methacholine concentration</th>
<th>Ref Pre Baseline Meas</th>
<th>0.0625 Level 1 Meas</th>
<th>0.25 Level 2 Meas</th>
<th>1.0 Level 3 Meas</th>
<th>4.0 Level 4 Meas</th>
<th>16.0 Level 5 Meas</th>
<th>Albuterol Post Meas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>2.6 10.6 42.2 170 680</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC Liters</td>
<td>4.92 4.15 4.07</td>
<td>4.15 4.16 3.58 3.42</td>
<td>2.31 4.26</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Ref</td>
<td>84 83</td>
<td>84 83 73 70 47 87</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Chg</td>
<td>-2</td>
<td>2 1 -12 -16 -43 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 Liters</td>
<td>4.10 2.98 2.93</td>
<td>3.00 2.92 2.92 2.81</td>
<td>1.90 3.08</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Ref</td>
<td>73 71</td>
<td>73 71 71 69 46 75</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Chg</td>
<td>-2</td>
<td>3 -0 -0 -4 -35 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEF25-75%</td>
<td>4.31 2.24 2.18</td>
<td>2.26 2.17 2.75 2.72</td>
<td>1.74 2.33</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Ref</td>
<td>52 51</td>
<td>52 50 64 63 40 54</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Chg</td>
<td>-3</td>
<td>4 -1 26 25 -20 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEF L/sec</td>
<td>9.56 7.74 7.64</td>
<td>7.69 7.28 6.74 5.69</td>
<td>4.68 7.83</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Ref</td>
<td>81 80</td>
<td>80 76 70 59 49 82</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Chg</td>
<td>-1</td>
<td>1 -5 -12 -26 -39 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Coding units 1 1 4 16 54

PD 20 FEV1: 345

Graph showing baseline and post values.
Example: APS Dosimeter Quadrupling Concentration

- Phillips Respironics SideStream disposable neb. # 4445
  - Min fill volume is 2 mL.
  - Compatible to the Jaeger MedicAid reusable neb.

- 10 tidal breaths

- APS device has a timer and breath counter
Integrated dosimeters / programs

• Potential advantages:
  – Breath counter
  – Flow sensing / visual
  – Timer
  – Calculation of PD/PC values
  – Filter to capture expired aerosol
### Dosimeters sequences-APS

#### Sequence - UW Tidal PD 20

<table>
<thead>
<tr>
<th>Step</th>
<th>Conc.</th>
<th>Dose</th>
<th>Substance</th>
<th>min</th>
</tr>
</thead>
<tbody>
<tr>
<td>R 1</td>
<td></td>
<td></td>
<td>Baseline</td>
<td>0</td>
</tr>
<tr>
<td>P 2</td>
<td>0.0625 mg/ml</td>
<td>1.5 ug</td>
<td>Methacholine</td>
<td>1.0</td>
</tr>
<tr>
<td>P 3</td>
<td>0.25 mg/ml</td>
<td>6 ug</td>
<td>Methacholine</td>
<td>1.0</td>
</tr>
<tr>
<td>P 4</td>
<td>1 mg/ml</td>
<td>24 ug</td>
<td>Methacholine</td>
<td>1.0</td>
</tr>
<tr>
<td>P 5</td>
<td>4 mg/ml</td>
<td>96 ug</td>
<td>Methacholine</td>
<td>1.0</td>
</tr>
<tr>
<td>P 6</td>
<td>16 mg/ml</td>
<td>384 ug</td>
<td>Albuterol MDI</td>
<td>15</td>
</tr>
<tr>
<td>D 7</td>
<td>4 Puffs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Response table - UW Tidal PD 20

<table>
<thead>
<tr>
<th>Seq.</th>
<th>FEV 1</th>
<th>%Ref.</th>
<th>Conc.</th>
<th>Dose</th>
<th>Cumul.</th>
<th>Breath</th>
</tr>
</thead>
<tbody>
<tr>
<td>*</td>
<td>2.927</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>R 2</td>
<td>2.878</td>
<td>98</td>
<td>0.0625 mg/ml</td>
<td>1.5 ug</td>
<td>1.5 ug</td>
<td>1.5 ug</td>
</tr>
<tr>
<td>P 3</td>
<td>3.004</td>
<td>103</td>
<td>0.25 mg/ml</td>
<td>6 ug</td>
<td>7.5 ug</td>
<td>10</td>
</tr>
<tr>
<td>P 4</td>
<td>2.600</td>
<td>89</td>
<td>1 mg/ml</td>
<td>24 ug</td>
<td>31.5 ug</td>
<td>10</td>
</tr>
<tr>
<td>P 5</td>
<td>2.713</td>
<td>93</td>
<td>4 mg/ml</td>
<td>96 ug</td>
<td>127.5 ug</td>
<td>10</td>
</tr>
<tr>
<td>P 6</td>
<td>2.066</td>
<td>71</td>
<td>16 mg/ml</td>
<td>384 ug</td>
<td>511.5 ug</td>
<td>10</td>
</tr>
<tr>
<td>D 7</td>
<td>2.917</td>
<td>100</td>
<td>4 Puffs</td>
<td></td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

**PD[-20]**

266.2 ug
Dosimeter sequences (APS)
Methacholine Challenge

10 Tidal Breath - APS Dosimeter Method

PD/PC[-20] FEV1: not reached

<table>
<thead>
<tr>
<th>Substance</th>
<th>Pred</th>
<th>Baseline</th>
<th>0.0625 mg/mL</th>
<th>0.25 mg/mL</th>
<th>1 mg/mL</th>
<th>4 mg/mL</th>
<th>16 mg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV 1</td>
<td>L</td>
<td>3.03</td>
<td>3.15</td>
<td>3.03</td>
<td>3.04</td>
<td>3.07</td>
<td>3.05</td>
</tr>
<tr>
<td>FEV 1% Chg/Base</td>
<td>%</td>
<td>0.0</td>
<td>-3.8</td>
<td>-3.5</td>
<td>-2.4</td>
<td>-3.1</td>
<td>-3.5</td>
</tr>
<tr>
<td>R at 5 Hz cmH2O/(L/s)</td>
<td>3.73</td>
<td>3.03</td>
<td>4.51</td>
<td>4.73</td>
<td>4.71</td>
<td>4.68</td>
<td>4.91</td>
</tr>
<tr>
<td>Resonant frequency</td>
<td>1/s</td>
<td>14.95</td>
<td>15.64</td>
<td>15.14</td>
<td>15.38</td>
<td>14.18</td>
<td>15.49</td>
</tr>
</tbody>
</table>

TECHNOLOGIST NOTES:
Pt. effort appeared maximal, Pt. was asymptomatic throughout testing.

Signed by Sue Murphy, RPFT 10/29/2018@1047
APS Dosimeter Single Concentration Option

- Load nebulizer with 16 mg/mL concentration
- 1, 2, 5, 13 breath sequence
- Has obvious conveniences
  - Less dilutions to mix
  - Less transfers of challenge substance
Procedure steps

• Allow 30 min room temp for solutions before use.
• Ensure equipment readiness/calibration
• Verify order, obtain informed consent
• Briefly explain procedure
• Obtain baseline pre-challenge measures
  – Spirometry
    • Raw or oscillometry (option)
Tidal Breathing: Diluent Step*

- Highly recommended step
- If FEV$_1$ changed is $<10\%$, go to conc #1
- If FEV$_1$ improved $>20\%$, repeat diluent step
- If FEV$_1$ decreased $\geq 20\%$, **stop challenge**

- Sterile normal saline
- Sterile normal saline with preservative
- Use of buffer is not recommended
Procedure steps*

• Aerosolize diluent and coach patient to breath “quietly” while wearing nose clip.
• After appropriate time or breaths turn off flow meter and remove neb.
• Perform post-diluent spiro at 30 and 90 seconds after the nebulization is completed.
• Obtain acceptable FEV1, report highest.
Procedure Steps*

• Target FEV1 is: highest FEV1 x 0.80
• Nebulize concentrations (low to high)
• Obtain post methacholine spirometry at 30 and 90 seconds after the nebulization is completed.
• Report highest FEV1 from acceptable trials.
  – Perform no more than 3 or 4 trials after each dose.
  – Full FVC is not required during trials.
  – No > than 3 min to perform trials
  – Time interval between 2 serial concentrations should be 5 min
• Proceed with steps until >20% decrease in FEV1 is observed, or the last concentration is achieved.

• If FEV1 decreases >20% stop challenge and give bronchodilator.

• Administer a rapid acting inhaled bronchodilator, wait 5-10 min.

• Consider flow volume loops prior to bronchodilator if VCD is suspected.

• Ensure FEV1 returns to pre-challenge range (within 90%)
Details you want to consider including:

- Medications
  - Cardiac and respiratory meds
- Reason for the test / Indications
- Symptoms reported
- Tabular data
  - Steps
  - Substance
  - Concentrations
  - Breaths
  - FEV1
  - Flow volume and volume time curves
  - Options: Airway resistance / Oscillometric data

**Methacholine Challenge Report**

<table>
<thead>
<tr>
<th>Step</th>
<th>Subst.</th>
<th>Conc</th>
<th>Dose</th>
<th>Brths</th>
<th>FEV1</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P2</td>
<td>Methacholine</td>
<td>0.062 mg/ml</td>
<td>1.5 ug</td>
<td>10</td>
<td>2.88</td>
</tr>
<tr>
<td>P3</td>
<td>Methacholine</td>
<td>0.25 mg/ml</td>
<td>6 ug</td>
<td>10</td>
<td>3.00</td>
</tr>
<tr>
<td>P4</td>
<td>Methacholine</td>
<td>1 mg/ml</td>
<td>24 ug</td>
<td>10</td>
<td>2.60</td>
</tr>
<tr>
<td>P5</td>
<td>Methacholine</td>
<td>4 mg/ml</td>
<td>96 ug</td>
<td>10</td>
<td>2.71</td>
</tr>
<tr>
<td>P6</td>
<td>Methacholine</td>
<td>16 mg/ml</td>
<td>384 ug</td>
<td>10</td>
<td>2.07</td>
</tr>
<tr>
<td>D7</td>
<td>Albuterol MDI</td>
<td>4 Puffs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Reporting of results**

PD[-20] FEV 1: 268.2 ug Dose
# Physician Interpretation

## Categorization of Airway Response to Methacholine

<table>
<thead>
<tr>
<th>PC20 (mg/mL)</th>
<th>PD20 (µg) microgram</th>
<th>PD20 (micromole)</th>
<th>AHR Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;16</td>
<td>&gt;400</td>
<td>&gt;2.0</td>
<td>Normal AHR</td>
</tr>
<tr>
<td>4-16</td>
<td>100-400</td>
<td>0.5-2</td>
<td>Borderline AHR</td>
</tr>
<tr>
<td>1-4</td>
<td>25-100</td>
<td>0.125-0.5</td>
<td>Mild AHR</td>
</tr>
<tr>
<td>0.25-1</td>
<td>6-25</td>
<td>0.3-0.125</td>
<td>Moderate AHR</td>
</tr>
<tr>
<td>&lt;0.25</td>
<td>1.5-6</td>
<td>0.008-0.03</td>
<td>Marked AHR</td>
</tr>
</tbody>
</table>
Billing / ICD coding: Methacholine Testing

- CPT code 95070 for administration of methacholine
- CPT code 94070: Multiple spirometric determinations bronchospasm eval
- J-7674: One unit for each mg of methacholine used
- JW-7674: One unit for each mg of methacholine discarded

How testing and supplies are billed can vary on setting (hospital or clinic).
Additional References

- Abstract: Developing Alternative Delivery System for Methacholine Challenge Tests, Allan L Coates, Kitty Leung, Sharon Dell, Bruce Culver
- El-Gammal, Killian, Scime, et al.; Relationship between Wright and AeroElipse Nebulizers 2015
Pitfalls to a quality methacholine BCT

- Staff are unfamiliar with steps and need more training/experience.
- Distractions during testing
- Equipment issues
- Medication dosing errors.
- Poor instruction/effort
- Deep breaths during dosing

- Practice or limit staff performing testing
- Minimize any phone use
- Use a timer
- Maintain equipment
- Use a worksheet / checklist

- Retrain seasoned staff.
Don’t forget to bring the FEV1 back up

**Protocol: BAN 6 Breath Tidal**

<table>
<thead>
<tr>
<th>Methacholine concentration</th>
<th>0.0625</th>
<th>0.25</th>
<th>1.0</th>
<th>4.0</th>
<th>16.0</th>
<th>Albuterol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ref</td>
<td>Pre Baseline</td>
<td>Level 1</td>
<td>Level 2</td>
<td>Level 3</td>
<td>Level 4</td>
</tr>
<tr>
<td></td>
<td>Meas</td>
<td>Meas</td>
<td>Meas</td>
<td>Meas</td>
<td>Meas</td>
<td>Meas</td>
</tr>
<tr>
<td>Dose</td>
<td>3.47</td>
<td>3.42</td>
<td>2.6</td>
<td>10.6</td>
<td>42.2</td>
<td>170</td>
</tr>
<tr>
<td>FVC Liters</td>
<td>3.38</td>
<td>3.34</td>
<td>3.12</td>
<td>3.12</td>
<td>2.85</td>
<td></td>
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<tr>
<td>% Ref</td>
<td>99</td>
<td>96</td>
<td>90</td>
<td>90</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>% Chg</td>
<td>-1</td>
<td>-2</td>
<td>-9</td>
<td>-9</td>
<td>-17</td>
<td></td>
</tr>
<tr>
<td>FEV1 Liters</td>
<td>2.72</td>
<td>2.48</td>
<td>2.48</td>
<td>2.46</td>
<td>2.38</td>
<td>2.20</td>
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<tr>
<td>% Ref</td>
<td>91</td>
<td>90</td>
<td>87</td>
<td>81</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>% Chg</td>
<td>-0</td>
<td>-1</td>
<td>-4</td>
<td>-11</td>
<td>-17</td>
<td></td>
</tr>
</tbody>
</table>

**Reminder:** Bring the FEV1 back up to 10% of baseline.
Don’t accept poor quality FVCs

16.0 mg/mL Metha

Pre / 16 mg/mL concentration
The future? Premixed concentrations

- Advantages
  - No time required for mixing
  - Standardized concentrations
  - Can reduce dosing errors
Summary / Predictions

- Methacholine testing using a **tidal breathing method and PD20** for characterization of AHR is the preferred method.

- Methacholine challenge helps assess airway reactivity.

- Many labs have adopted the BAN nebulizer for challenge testing.

- Characterization of alternative nebulizers is increasing.
- Pre-mixed FDA approved methacholine concentrations (when available) will help standardize testing.

- Labs need adapt to the current methacholine testing standard, update policies, retrain and monitor competency.
Tools you can use

The remaining 7 slides in this presentation include:
- Worksheet example for use during testing
- Training and competency assessment tool
- Manufacturer on-line training tools and courses
- Interpretation scripts for physicians
Methacholine Challenge Sheet

Breaths: 6 6 6 6 6 6

Baseline FEV1 2.86
Repeateable? Y N
X .80
Med / Allergies reviewed? Y N
20% change 2.28

Pretest probability: wheezing, dyspnea, chest tightness, cough...
- During respiratory infections
- With exposure to cold
- After exercise
- Following inhalant exposures at work or with activities

Signs / Symptoms during testing: YES CHEST THROAT TIGHTNESS

Patient effort: Poor Fair Good Excellent

4.0 mg/mL Dose

M. OBrien 2018 Methacholine Worksheet
### Annual Competency Assessment / Training --- Bronchial Challenge Test — Methacholine

**Core competencies**

2. Understands dilution scheme used in our lab.
3. Obtains methacholine dilutions from pharmacy and allows to equilibrate to room temp.
4. Calibrates pulmonary testing system
5. Demonstrates understanding of workflow for BCT
   a. Verifies order
   b. Assesses appropriateness of testing.
   c. Allergy and medication review in EMR.
   d. Reviews possible contraindications.
   e. Briefly explains testing procedure to the patient
   f. Obtains signed consent form.
   g. Obtains acceptable and repeatable baseline spirometry (resistance optional).
   h. Calculates 20% fall in FEV1.
   i. Demonstrates clean technique when transferring concentrations for nebulization.
   j. Encourages tidal breathing during dosing and minimizes any TLC maneuvers.
   k. Monitors time appropriately between dosing, Spiro, dosing....
   l. Recognizes a 20% decrease in FEV1.
   m. Administers bronchodilators via nebulizer or MDI.
   n. Assess response to inhaled bronchodilator.
   o. Output of report with appropriate technologist notes.
   p. Post PDF in EMR.
   q. Charge for technical component.
6. New staff: Four days of supervised testing / practice and 20 supervised tests.
7. Experienced staff: 1 day of supervised testing.
8. Is familiar with safety and emergency procedures.

### Questions: True / False

1. PD20 is now preferred over PC20 to characterize the response to methacholine. **T** **F**
2. Methacholine is a direct airway challenge that mimics the response of acetylcholine with muscarinic receptors on airway smooth muscle. **T** **F**.
3. It is ok to test a patient with a history of uncontrolled HTN when the systolic BP is >200 mmHg and systolic BP is 90 mmHg. **T** **F**.
4. A primary contraindication to performing bronchial challenge testing is:
5. Changes in airway resistance parameters can help confirm changes observed in FEV1. **T** **F**.
ATS Short (quadrupling) Doses

*Please note: the following is not contained in the US Product Insert.*

**Concentrations of:**

- 16 mg/mL
- 4 mg/mL
- 1 mg/mL
- 0.25 mg/mL
- 0.0625 mg/mL

**ATS Short Dilution Aid**

**ATS Short Dilution Video**

https://provocholine.com/
Step 1. – Preparing Vial A, 25 mg/mL solution

1. Using the diluent needle and syringe, draw 4 mL of diluent and trans

For any questions please contact Methapharm at 1-800-287-7686 ext. 7801

or visit www.provocholine.com to download additional resources
Welcome to Methapharm’s training courses for methacholine challenge testing.

The purpose of these courses is to assist healthcare professionals and facilities with the implementation of methacholine challenge testing service and to provide a “ready to use” QA program for those currently providing the service. There are three different modules in this program each with their own study material, as well as their own post test evaluations. If you have any questions or require assistance please contact us.

- Taking the Provocholine Challenge ➔ (2.0 CRCE credit hours)
- Reconstituting Provocholine for Methacholine Challenge Testing ➔ (1.0 CRCE credit hour)
- Performing a Methacholine Challenge Test ➔ (1.0 CRCE credit hour)
**Negative** \((PC20>16\) or \(PD20>400\))

The baseline FEV1 of ______ is in a normal range and greater than predicted. The shape of the flow volume curve is linear at baseline and throughout the challenge.

After ____ breaths of 16\(\text{mg/mL}\) concentration of methacholine there was a _____% decrease/ increase in FEV1 and no significant change in airway resistance parameters. Following administration of the bronchodilator there was no change/_____% increase in FEV1 and normalization of airway resistance.

This is a negative methacholine challenge.

Methacholine challenge testing is more useful in excluding a diagnosis of asthma than establishing one because its negative predictive value, when respiratory symptoms are present, is greater than its positive predictive.
**Borderline, Mild, Moderate, Marked**

The baseline FEV1 of ______ is ______% of predicted. The shape of the flow volume curve is linear / slightly curvilinear at baseline.

After inhalation of the 0.0625, 0.25, 1, 4, 16 mg/mL concentration the FEV1 decreased ________%.
The calculated PD20 is ________.

Changes observed in airway resistance confirm the decrease observed in FEV1.

Based on the PD20 of ________ micrograms, the response to methacholine is categorized as:

<table>
<thead>
<tr>
<th>Response</th>
<th>PD20</th>
<th>PC20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borderline AHR</td>
<td>100-400</td>
<td>4-16</td>
</tr>
<tr>
<td>Mild AHR</td>
<td>25-100</td>
<td>1-4</td>
</tr>
<tr>
<td>Moderate AHR</td>
<td>6-25</td>
<td>0.25-1</td>
</tr>
<tr>
<td>Marked AHR</td>
<td>1.5-6</td>
<td>&lt;0.25</td>
</tr>
</tbody>
</table>

Following bronchodilator administration, the FEV1 returned to baseline / increased from baseline.

Airway resistance parameters also normalized / improved following bronchodilatation.

Clinical correlation is required.
Thank you! Questions

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Focus on Respiratory Care, Sleep Medicine & Pulmonary Diagnostics

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